Diffusion-Weighting Attenuates the BOLD Peak Signal Change but not the Post-Stimulus Undershoot

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Purpose: To test whether the post-stimulus undershoot of the BOLD signal during brain activation is consistent with elevated blood volume that is slow to return to baseline.

Background: Brain neural activation induces localized changes in cerebral blood flow (CBF), cerebral metabolic rate of O2 (CMRO2), and cerebral blood volume (CBV). The temporal response of the Blood Oxygenation Level Dependent (BOLD) signal used to map patterns of brain activation depends on the dynamics of all three of these physiological quantities. Numerical studies suggest that the BOLD signal change has contributions from both the extravascular space [1], which primarily depends on changes in the total voxel deoxyhemoglobin (dHb) content, and also from the intravascular space [2], which primarily depends on the dHb concentration in blood. The BOLD response often shows a distinct post-stimulus undershoot that is not present in the flow signal measured with arterial spin labeling [3,4]. This transient BOLD effect could be due to increased O2 extraction above baseline [5], or to a slower return of CBV to its resting value. The latter view is supported by recent experimental work in rats [6], and we recently proposed a kinetic model (the Balloon Model [7]) to show how such transients can arise due to blood volume effects even when CBF and CMRO2 are tightly coupled. The hypothesis of coupled CBF and CMRO2 with slowly resolving CBV changes leads to a testable prediction: if CBF and CMRO2 have returned to normal resting values, then the post-stimulus undershoot should be due only to the extravascular signal, because the total dHb content is elevated but the concentration of dHb in blood has returned to baseline. In this report we present the results of an initial experimental test of this prediction.

Experimental Methods and Results: For this visual stimulation study, subjects (n=3) wore Grass goggles to view a flashing (8 Hz) grid of red lights. The stimulus was applied for 20 sec, followed by a 40 sec rest period. Each run consisted of 8 repeats of this 1 min cycle, and a total of 8 runs were performed in each subject. Imaging was done on a 3T Bruker Biospec system with a local head gradient/rf coil. Two sagittal slices were acquired on either side of the midline using a gradient echo EPI pulse sequence with TR=1010.1 ms, TE=52 ms, FOV=24 cm, slice thickness=8 mm, and a 64x64 matrix. On alternate runs diffusion-weighting bipolar gradient pulses (2.45 G/cm, 25 ms total duration) were added to destroy the vascular signal. All images were coregistered with IMREG (MCW) and the runs with and without diffusion weighting were separately averaged together (4 runs each). For each pixel time course a third order polynomial baseline drift was removed, and the data were then collapsed over the 8 cycles to produce a time series for one cycle of stimulus presentation. The TR was chosen to be slightly asynchronous with the stimulus presentation so that the time resolution of the collapsed time series was improved by a factor of 8. However, remaining low frequency drifts in the full time series are converted to high frequency noise in the collapsed time series, so gaussian smoothing with a FWHM=0.5s was applied to the final data. For each subject, all voxels showing a signal change greater than 1% during the stimulus were selected and averaged (Fig 1).

Discussion: With no diffusion-weighting, the BOLD response showed a strong positive signal change with a pronounced post-stimulus undershoot. Added diffusion-weighting reduced the peak BOLD change by about 37%, but did not attenuate the post-stimulus undershoot. This data suggests that at 3T there is a significant intravascular contribution to the BOLD signal. The lack of attenuation of the undershoot is consistent with the hypothesis that the undershoot is a purely extravascular signal change that occurs after CBF and CMRO2 have returned to baseline values, but before the CBV changes have fully resolved. As an illustration, Fig. 2 shows curves calculated from the Balloon Model [7], which is based on this hypothesis, with parameters adjusted to approximate the data. Model parameters used were: resting O2 extraction of 40%, resting blood volume fraction of 1.5%, steady-state power law relation between volume and flow with exponent 0.4. The dynamic curve of outflow lags behind inflow. The dashed curve is the BOLD signal with complete elimination of intravascular signal. The curves of CBF, CMRO2, and CBV that produce the model BOLD curves are shown in the lower panel. In the model curves the post-stimulus BOLD signal crosses zero slightly earlier when the blood signal is attenuated, and the measured data also shows this pattern.

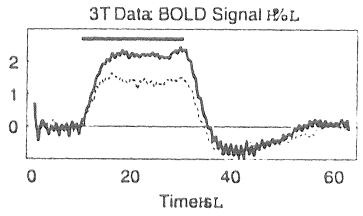

Figure 1. 3T visual stimulation data: with (dashed) and without (solid) diffusion weighting.

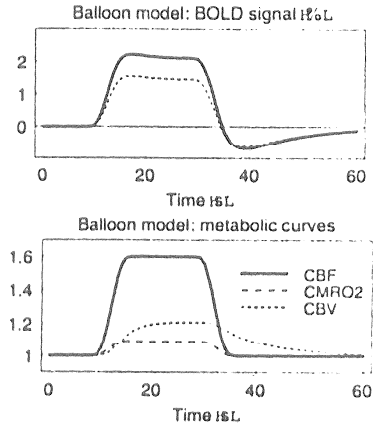

Figure 2: Illustrative balloon model calculations.

Conclusions: These data are consistent with the hypothesis that CBF and CMRO2 changes resolve quickly after the end of the stimulus, but the blood volume resolves more slowly. For the alternative hypothesis of increased O2 extraction in the post-stimulus period, we would expect that the altered dHb concentration in blood would also produce an undershoot in the intravascular signal, and that diffusion-weighting would then attenuate the undershoot as well.

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